Direct Cardiac Reprogramming for Heart Regeneration

Grant Award Details

Direct Cardiac Reprogramming for Heart Regeneration

Grant Type: Early Translational III

Grant Number: TR3-05593

Project Objective: The development candidate is a gene therapy to regenerate cardiac myocytes following MI. The DC will work by converting cardiac fibroblasts to working cardiac myocytes by delivering AAV packaged cardiac transcription factors.
Objective = Cardiac regeneration. The first test of the technology will be in the semi acute setting, with the longer-term goal of treating CHF. Two critical milestones are identification of the proper factors for human (vs mouse) reprogramming and identification of a vector that selectively infects fibroblasts vs myocytes at adequate efficiency to drive the reprogramming event. Organ specificity will likely be route driven and need in vivo demonstration. In short, the program carries the risks inherent to gene therapy, but has the potential to be paradigm shifting if these are overcome.

Investigator:

Name:	Deepak Srivastava
Institution:	Gladstone Institutes, J. David
Type:	PI

Disease Focus: Heart Disease

Human Stem Cell Use: Directly Reprogrammed Cell

Award Value: $5,795,871

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period:	Year 3
View Report	

Reporting Period:	Year 4 (NCE)
View Report	

Grant Application Details

Application Title: Direct Cardiac Reprogramming for Heart Regeneration

Public Abstract: Heart disease is a leading cause of mortality. The underlying pathology is typically loss of heart muscle cells that leads to heart failure. Because heart muscle has little or no regenerative capacity after birth, current therapeutic approaches are limited for the over 5 million Americans who suffer from heart failure. Our recent findings regarding direct reprogramming of a type of structural cell of the heart, called fibroblasts, into cardiac muscle-like cells using just three genes offers a novel approach to achieving cardiac regeneration. 50% of cells in the human heart are cardiac fibroblasts, providing a potential source of new heart muscle cells for regenerative therapy. We simulated a heart attack in mice by blocking the coronary artery, and have been able to reprogram existing mouse cardiac fibroblasts in to new muscle by delivering the three genes into the heart. We found a significant reduction in scar size and an improvement in cardiac function that persists after injury. The reprogramming of cells in the intact organ was more complete than in cells in a dish. We now propose to develop the optimal gene therapy approach to introduce cardiac reprogramming genes into the heart, to establish the optimal delivery approach to administer virus encoding cardiac reprogramming factors that results in improvement in cardiac function in a preclinical model of cardiac injury, and to establish the safety profile of in vivo cardiac reprogramming in a preclinical model.

Statement of Benefit to California: This research will benefit the state of California and its citizens by helping develop a new therapeutic approach to cardiac regeneration. Heart disease is a leading cause of death in adults and children in California, but there is no current treatment that can promote cardiac regeneration. This proposal will lay the groundwork for a clinical trial that could result in generation of new heart muscle cells from within the heart. If successful, there is potential economic benefit in terms of productive lives saved and in the commercialization of this technology.